(b) analyzing the metabolites that passed through the membrane into a second solution to assess drug metabolism.

REMARKS

I. Status of the Claims

Claims 1-5 and 7-12 are cancelled.

Claims 13-29 are added.

Claims 13-29 are pending.

II. Support for the Claim Amendments

Page	Line	Comments
1	7	high throughput
	8-1	drug development and screening for metabolic parameters, bioactivation and potential toxicity
2	11-14	"The method is a novel, high-throughput, on-line analysis of compounds added to a continuous flow system through biological materials in solution-that interact with the compounds. 'High-throughput' is defined herein to be of the order of 1 metabolite (compound) processed per minute or more."
2-3		definition of -supportive solution -continuous flow -predetermined characteristics -suitable conditions - kit
4	FIG. 1A	"on line screening for metabolism and toxicity or bioavailability of a compound"
	FIG. 2	"screen xenobiotic compounds for products of drug metabolism"
	FIG. 4	
5	FIG. 7	
6	6-16	summary of invention
6	17-34	summary of invention
8	7-8	"generating metabolites, extracting them from the biological material, and then analyzing them."

Page	Line	Comments
		reactive metabolites, toxic screens
8	20-33	live cells for absorption studies (bioavailability)
9	1-2	"one compound or one mixture of compounds
12	33-34	"investigate complex metabolism pathways or to investigate bioavailability"
14	33-34	metabolites used to study
15	1-3	metabolites used to study
Example	1	
Example	2	

III. Venton is Not an Anticipating Publication and Common Ownership Prevents a 102(e)/103 Rejection

Venton does not anticipate the present claims because Venton does not have all the elements of any claim. Venton determines whether compounds to be tested are bound or unbound to a biological sample by analyzing what unbound products are able to cross the membrane. As claim 1 states:

> (b) separating non-bound compounds from the bound compound by passing the non-bound compounds through the ultrafiltration membrane and discarding the non-bound compounds;
>
> (c) releasing the bound compound from the macromolecule wherein the macromolecule remains in solution for reuse to the binding side of the ultrafilitration membrane, and wherein the released compound passes through the ultrafilitration membrane;

According to [MPEP, 706.02(I)(1)]:

> Effective November 29, 1999, subject matter which was prior art under former 35 U.S.C. 103 via 35 U.S.C. 102(e) is now disqualified as prior art against the claimed invention if that subject matter and the claimed invention" were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Recorded assignments are filed as Exhibits A and B to show support for 103(c).

IV. Summary and Conclusion

Claims are formatted to have consistent terminology. Therefore, the claims should not be subject to 35 U.S.C. first and second paragraph rejections.

Also, as discussed during the interviews, the 102 and 103 rejections based on Venton

should be removed because Venton does not have all the claimed elements as required for a 102 rejection and Venton addressed drug discovery based on analysis of bound vs. unbound drug candidates which passed through a membrane. In the present invention, drug development issues such as drug metabolism, toxicity and bioavailability are addressed instead of drug discovery. In the present invention, the first solution remains on one side of the membrane, reactions occur that do not bring the initial biological material across the membrane, and products such as drug metabolites or glutathione adducts of reactive drug metabolites cross the membrane into the second solution where they are analyzed.

Applicant request allowance of claims 13-29.

Please contact applicants' representative if you have any questions.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 10-0435 with reference to our attorney docket number (21419/90368).

Respectfully submitted,

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Registration No. 35,601

December 3, 2002

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SERIAL NO. 09/471,523
ATTY DOCKET NO. 21726/90386

WE CLAIM

[1. A method for determining whether a compound from a sample has predetermined characteristics that would make it suitable for a specific purpose, said purpose comprising drug development and screening for metabolic parameters, said method comprising:

a. obtaining a biological material in a first solution or suspension;

b. inducing a flow of a supportive solution through the first solution or suspension;

c. adding the sample to the continuous flow of the supportive solution;

d. reacting the biological material in the first solution or suspension with the compound in the sample to provide metabolites, or to assess permeability and bioavailability;

e. washing the results of the reacting between the biological material in the first solution and the compound in the sample through an ultrafiltration membrane to form a second solution; and

f. analyzing the second solution to determine whether the compound in the sample has the predetermined characteristics, wherein the predetermined characteristics are selected for the group consisting of functioning as a substrate for an enzyme, showing desirable rates of enzymatic catalysis, showing desirable rates of cell permeability or transport, and showing enzymatic activation to reactive or toxic metabolites.

2. The method of claim 1, wherein the biological material is selected from a group consisting of a protein, a peptide, an oligonucleotide, an oligosaccharide, a microsome, a cell, a tissue, an enzyme, a receptor, DNA and RNA.

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3. The method of claim 1, wherein the compound is selected from the group consisting of a natural product, a combinatorial library, a drug, a drug mixture, a xenobiotic compound, a mixture of xenobiotic compounds, an endogenous compound, and a mixture of endogenous compounds.

4. The method of claim 1, wherein the supportive solution is selected from a group consisting of a buffer, a nutrient medium, or a combination thereof, said supportive solution maintaining the biological material in a state wherein the biological material interacts with a compound in the sample.

5. The method of claim 1, wherein the continuous flow facilitates the reacting of the biological material with the sample in the first solution or suspension and facilitates the removal of compounds from the sample by washing them through the ultrafiltration chamber into the second solution.

7. The method of claim 1, wherein the sample is added to the continuous flow by means of injection.

8. The method of claim 1, wherein the suitable conditions for reacting of the biological material in the first solution with the compound in the sample comprises mixing the sample with the biological material to achieve a homogeneous distribution of sample, temperature control to maintain function of the biological material, adequate concentration of sample and sufficient amount of biological material to facilitate analysis, sufficient time for interaction, and control of atmospheric gases (oxygen and carbon dioxide) to maintain function of the biological material.

9. The method of claim 1, wherein the ultrafiltration membrane has pore sizes that allow the sample molecules to pass through but not the biological material.

10. The method of claim 1, wherein the analyzing of the second solution is by mass spectrometry.

11. A kit for analyzing a compound in a sample, to determine whether the compound has predetermined characteristics that would make it suitable for a specific purpose, said purpose comprising drug development and screening for metabolic parameters, said kit comprising in

separate containers, an ultrafiltration membrane, a first solution containing a biological material, a buffer, a test solution, and a set of standard solutions with predetermined characteristics wherein the predetermined characteristics consist of functioning as a substrate for an enzyme, showing desirable rates of enzymatic catalysis, and showing desirable rates of cell permeability or transport, showing enzymatic activation to reactive or toxic metabolites.

12. The method of claim 1, wherein multiple chambers with ultrafiltration membranes are arranged in parallel with a single mass spectrometer for steps e and f.]

13. A high throughput method for determining whether a compound or mixture of compounds is suitable for intended use as a drug or a natural product, said method comprising:

(a) placing a first solution comprising biological material having higher molecular weights than the compounds or mixture of compounds, into an ultrafiltration chamber, said chamber comprising a membrane with pore sizes that will not allow passage of the biological material out of the chamber;

(b) placing the compound or mixture of compounds into the ultrafiltration chamber, said chamber comprising a membrane with pore sizes that allow passage of the compound or mixture of compounds out of the chamber;

(c) providing a supportive solution to the ultrafiltration chamber that facilitates reactions between the biological material and the compound or mixtures of compounds to produce products of the reactions wherein the ultrafiltration chamber allows passage of the products out of the chamber to form a second solution, but does not allow passage of the biological materials;

(d) analyzing the second solution comprising the products of the reactions between the biological material and the compound or mixture of compounds, to determine whether the compound or any of the mixture of compounds is suitable for use as a drug or natural product.

14. The method of claim 13, wherein the biological material is selected from a group

consisting of a protein, a peptide, an oligonucleotide, an oligosaccharide, a microsome, a cell, a tissue, an enzyme, DNA and RNA.

15. The method of claim 13, wherein the compound or mixture of compounds is selected from the group consisting of a natural product, a combinatorial library, a drug, a drug mixture, a xenobiotic compound, a mixture of xenobiotic compounds, an endogenous compound, a mixture of natural products, and a mixture of endogenous compounds.

16. The method of claim 13, wherein the supportive solution is selected from a group consisting of a buffer, a nutrient medium, or a combination thereof, said supportive solution maintaining the biological material in a state wherein the biological material reacts with a compound or mixture of compounds in the sample.

17. The method of claim 16, wherein the supportive solution facilitates the reactions of the biological material with the first solution and facilitates the removal of compounds, or mixture of compounds and products of the reactions between the compound or mixture of compounds and the biological material, by washing them through the ultrafiltration chamber into the second solution.

18. The method of claim 13, wherein the compound or mixture of compounds is added by means of injection.

19. The method of claim 13, wherein the suitable conditions for reactions between the biological material in the first solution with the compound or mixture of compounds, comprises mixing the sample with the biological material to achieve a homogeneous distribution of sample, controlling temperature to maintain function of the biological material, providing adequate concentration of sample and sufficient amount of biological material to facilitate analysis, providing sufficient time for interaction, and controlling atmospheric gases to maintain function of the biological material.

20. The method of claim 13, wherein the analyzing of the second solution is by mass spectrometry.

21. The method of claim 13, wherein the products of the reactions comprise metabolites, glutathione adducts, and small molecules to determine cellular absorption.

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22. The method of claim 13, wherein multiple chambers with ultrafiltration membranes are arranged in parallel with a single mass spectrometer for step d.

23. A kit for analyzing a compound or mixture of compounds to determine if a compound or any of the mixture of compounds are suitable for use as a drug or natural product, by analyzing reaction products between biological material and the compound or mixture of compounds, said kit comprising in separate containers, (a) an ultrafiltration membrane with pore sizes that allow passage of the compound or mixture of compounds and reaction products, but not passage of the biological material, (b) a first solution containing the biological material, and (c) standards against which to compare analysis of the products of reactions between the first solution and the compounds or mixture of compounds to determine suitability as a drug or natural product.

24. A high throughput method for determining characteristics of a compound or mixture of compounds, the method comprising:

(a) interacting the compound with a biological material in a first solution or suspension to form products;

(b) providing an ultrafilitration membrane in contact with the first and a second solution with pores of suitable size to allow the products to pass from the first solution through the membrane into the second solution; and

(c) analyzing the products in the second solution.

25. The method of claim 24, wherein the compound in the first solution is a drug, the biological material that interacts with the drug is selected from the group consisting of cytochrome P40, UDP-glucuronyltransferases, and glutathione transferase, and analysis is by pulsed ultrafiltration mass spectrometry.

26. The method of claim 24, wherein the first solution comprises chlorpromazine and rat liver microsomal cytochrones P450, NADPH is added, and results of chlorpromazine oxidation are analyzed by pulsed ultrafiltration positive ion electroscopy mass spectrometry.

27. The method of claim 24, wherein rat liver microsomes containing cytochrome P450 and microsomal glutalthione S-transfease interact with butydimethyl phenol, NADPH and

glutathione on the first solution side of the ultrafiltration membrane, and metabolites produced by the interaction pass through the membrane into a second solution for analysis by negative ion electroscopy-mass spectrometry, wherein the metabolite quinine methide reacts with water or with glutathione to for an adduct.

28. The method of claim 24, wherein epithelial cells and xenobiotic compounds are in the first solution, compounds that are excluded from entering the cells elute first through the ultrafiltration membrane, compounds that enter the cells may elute later, and analysis of bioavailability is determined by inverse correlation with eluting time.

29. A method to assess drug metabolism using a high throughput system, the method comprising:

(a) interacting the drug with hepatic microsomes and the cofactor NADPH in a first solution on one side of an ultrafiltration membrane with pore sizes that allow all metabolites to pass through to the other side; and

(b) analyzing the metabolites that passed through the membrane into a second solution to assess drug metabolism.

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WE CLAIM

13. A high throughput method for determining whether a compound or mixture of compounds is suitable for intended use as a drug or a natural product, said method comprising:

(a) placing a first solution comprising biological material having higher molecular weights than the compounds or mixture of compounds, into an ultrafiltration chamber, said chamber comprising a membrane with pore sizes that will not allow passage of the biological material out of the chamber;

(b) placing the compound or mixture of compounds into the ultrafiltration chamber, said chamber comprising a membrane with pore sizes that allow passage of the compound or mixture of compounds out of the chamber;

(c) providing a supportive solution to the ultrafiltration chamber that facilitates reactions between the biological material and the compound or mixtures of compounds to produce products of the reactions wherein the ultrafiltration chamber allows passage of the products out of the chamber to form a second solution, but does not allow passage of the biological materials;

(d) analyzing the second solution comprising the products of the reactions between the biological material and the compound or mixture of compounds, to determine whether the compound or any of the mixture of compounds is suitable for use as a drug or natural product.

14. The method of claim 13, wherein the biological material is selected from a group consisting of a protein, a peptide, an oligonucleotide, an oligosaccharide, a microsome, a cell, a tissue, an enzyme, DNA and RNA.

15. The method of claim 13, wherein the compound or mixture of compounds is selected from the group consisting of a natural product, a combinatorial library, a drug, a drug mixture, a xenobiotic compound, a mixture of xenobiotic compounds, an endogenous compound, a mixture of natural products, and a mixture of endogenous compounds.

16. The method of claim 13, wherein the supportive solution is selected from a group consisting of a buffer, a nutrient medium, or a combination thereof, said supportive solution maintaining the biological material in a state wherein the biological material reacts with a

compound or mixture of compounds in the sample.

17. The method of claim 16, wherein the supportive solution facilitates the reactions of the biological material with the first solution and facilitates the removal of compounds, or mixture of compounds and products of the reactions between the compound or mixture of compounds and the biological material, by washing them through the ultrafiltration chamber into the second solution.

18. The method of claim 13, wherein the compound or mixture of compounds is added by means of injection.

19. The method of claim 13, wherein the suitable conditions for reactions between the biological material in the first solution with the compound or mixture of compounds, comprises mixing the sample with the biological material to achieve a homogeneous distribution of sample, controlling temperature to maintain function of the biological material, providing adequate concentration of sample and sufficient amount of biological material to facilitate analysis, providing sufficient time for interaction, and controlling atmospheric gases to maintain function of the biological material.

20. The method of claim 13, wherein the analyzing of the second solution is by mass spectrometry.

21. The method of claim 13, wherein the products of the reactions comprise metabolites, glutathione adducts, and small molecules to determine cellular absorption.

22. The method of claim 13, wherein multiple chambers with ultrafiltration membranes are arranged in parallel with a single mass spectrometer for step d.

23. A kit for analyzing a compound or mixture of compounds to determine if a compound or any of the mixture of compounds are suitable for use as a drug or natural product, by analyzing reaction products between biological material and the compound or mixture of compounds, said kit comprising in separate containers, (a) an ultrafiltration membrane with pore sizes that allow passage of the compound or mixture of compounds and reaction products, but not passage of the biological material, (b) a first solution containing the biological material, and (c) standards against which to compare analysis of the products of reactions between the first solution and the compounds or mixture of compounds to determine suitability as a drug or

natural product.

24. A high throughput method for determining characteristics of a compound or mixture of compounds, the method comprising:

(a) interacting the compound with a biological material in a first solution or suspension to form products;

(b) providing an ultrafilitration membrane in contact with the first and a second solution with pores of suitable size to allow the products to pass from the first solution through the membrane into the second solution; and

(c) analyzing the products in the second solution.

25. The method of claim 24, wherein the compound in the first solution is a drug, the biological material that interacts with the drug is selected from the group consisting of cytochrome P40, UDP-glucuronyltransferases, and glutathione transferase, and analysis is by pulsed ultrafiltration mass spectrometry.

26. The method of claim 24, wherein the first solution comprises chlorpromazine and rat liver microsomal cytochrones P450, NADPH is added, and results of chlorpromazine oxidation are analyzed by pulsed ultrafiltration positive ion electroscopy mass spectrometry.

27. The method of claim 24, wherein rat liver microsomes containing cytochrome P450 and microsomal glutalthione S-transfease interact with butydimethyl phenol, NADPH and glutathione on the first solution side of the ultrafiltration membrane, and metabolites produced by the interaction pass through the membrane into a second solution for analysis by negative ion electroscopy-mass spectrometry, wherein the metabolite quinine methide reacts with water or with glutathione to for an adduct.

28. The method of claim 24, wherein epithelial cells and xenobiotic compounds are in the first solution, compounds that are excluded from entering the cells elute first through the ultrafiltration membrane, compounds that enter the cells may elute later, and analysis of bioavailability is determined by inverse correlation with eluting time.

29. A method to assess drug metabolism using a high throughput system, the method comprising:

(a) interacting the drug with hepatic microsomes and the cofactor NADPH in a first solution on one side of an ultrafiltration membrane with pore sizes that allow all metabolites to pass through to the other side; and

(b) analyzing the metabolites that passed through the membrane into a second solution to assess drug metabolism.